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Nonmetastatic Ewing family tumors: high-dose chemotherapy with stem cell rescue in poor responder patients. Results of the Italian Sarcoma Group/ Scandinavian Sarcoma Group III protocol

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Background: High-dose chemotherapy (HDT) was added to conventional chemotherapy in Ewing sarcoma family tumor (EFT) patients, poor responders (PRs) to induction chemotherapy in order to improve their survival.

Patients and methods: Patients aged ≤40 years with nonmetastatic Ewing sarcoma (ES) received vincristine (V), doxorubicin (A), cyclofosfamide (C), actinomycin (Ac), ifosfamide (I) and etoposide (E) (VACAc-IE regimen) as induction chemotherapy. As maintenance treatment, good responders (GR) received nine cycles of VACAc-IE regimen. PRs received three cycles of VAC-IE, mobilizing cycle with CE and HDT with Busulfan and Melphalan with stem cell support.

Results: Three hundred patients [median age 15 years (3–40 years)] entered the study. One patient refused local treatment, 242 (81%) underwent surgery [with radiotherapy (RT) in 80] and 57 (19%) RT alone. No toxic deaths were recorded. Overall GR were 146 (49%). Twenty-eight PR did not receive HDT. At a median follow-up of 64 months (21–116 months), 5-year overall and event-free survival (EFS) were 75% and 69%, respectively. Five-year EFS was 75% for GR, 72% for PR treated with HDT and 33% for PR who did not receive HDT.

Conclusions: High-dose therapy added to the VACA-IE regimen in PR patients is feasible and effective. Selected groups of patients with ES can benefit from HDT.

Key words: chemotherapy-induced necrosis, Ewing sarcoma, high-dose chemotherapy

introduction

Ewing sarcoma family tumors (EFT) are rare small round cell tumors arising either in bone or soft tissues. Usually, they occur in children, adolescents and young adults, and in these age groups, they are the second most common bone cancer [1].

Chemotherapy treatment of patients with EFT has been based for decades on a four-drug combination of vincristine, doxorubicin, cyclophosphamide and actinomycin D (VACAc regimen) [2, 3]. Some studies replaced cyclophosphamide with ifosfamide, and others added ifosfamide and/or etoposide [4–7]. A randomized study comparing the VACAc regimen with the VACAc + ifosfamide/etoposide (VACAc/IE) combination demonstrated that in nonmetastatic patients, the six-drug regimen offers the best survival probability [8]. Recurrence can be expected in >30% of patients [4, 8–10]. Retrospective analyses have shown that chemotherapy-induced tumor necrosis is predictive of survival [4, 7, 9, 11, 12], suggesting the need of a different chemotherapy strategy in patients showing poor sensitivity to primary chemotherapy.

In the nineties, several studies with the use of high-dose chemotherapy (HDT) followed by autologous stem cell

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reconstitution reported interesting, although, contradictory results [13–21].

In 1999, the Italian Sarcoma Group (ISG) and the Scandinavian Sarcoma Group (SSG) activated a joint study. Treatment strategy was based on the primary use of the six drugs, active against EFT. For poor responder (PR) patients, treatment intensification with the addition of HDT was added. The results of this study are reported here.

patients and methods

Patient selection

Patients aged ≤40 years with biopsy-proven histological diagnosis of EFT without synchronous metastases were eligible for the study.

Written informed consent was obtained before starting the protocol. Presence of synchronous metastases [as assessed by means of technetium bone scan, computed tomography (CT) of the chest and bone marrow aspirates], medical contraindication to the drugs used in the protocol and a delay of >4 weeks from biopsy to beginning of treatment were exclusion criteria.

All patients had a biopsy-proven diagnosis of Ewing sarcoma (ES)/primitive neuroectodermal tumor carried out by a pathologist from the referral centers (ISG) or confirmed by expert pathology panel (SSG).

Pretreatment tumor evaluation included conventional X-rays, CT and/or magnetic resonance imaging of the entire involved bone. These were repeated after primary chemotherapy, before local treatment. The stage of the disease was assessed by means of technetium bone scan, CT of the chest and bone marrow aspirates and biopsy.

study design

The ISG/SSG III study identified two different risk groups of patients on the basis of tumor response to primary chemotherapy.

All patients underwent primary chemotherapy consisting of the six drugs: vincristine (V), doxorubicin (A), cyclophosphamide (C), actinomycin (Ac), ifosfamide (I) and etoposide (E).

After primary chemotherapy, tumor assessment, local control procedures and evaluation of tumor response were centralized in referral centers.

Surgery was the preferred treatment of local control. Radiotherapy (RT) alone was reserved for tumors where the possibility achieving adequate surgical margins was excluded. Tumor response assessment was based on evaluation of the grade of primary chemotherapy-induced tumor necrosis for surgery or on radiographic tumor regression for those patients who received RT as local treatment only.

Good responder (GR) patients continued treatment with the same drugs delivered in the primary phase. PR patients underwent 'salvage' chemotherapy with the addition of HDT and peripheral blood stem cells support.

The study protocol was approved by the ethical committee of the participating institutions.

treatment plan

The chemotherapy outline is reported in Figure 1.

The use of HDT was excluded in case of tumor progression during chemotherapy. A minimum CD34+ cell harvest of 2.5×10^6/kg was requested to proceed to the high-dose treatment.

Local therapy was planned after four courses of primary chemotherapy. Surgery was the treatment of choice and when site or dimensions excluded the possibility of adequate surgical margins, radiotherapy alone was given. The total radiation dose was 54 Gy, 1.5 Gy twice daily, 5 days/week/36 fractions. When surgical margins were inadequate, postoperative radiotherapy was recommended with a total dose of 42 Gy (1.5 Gy twice daily, 5 days/week/28 fractions).

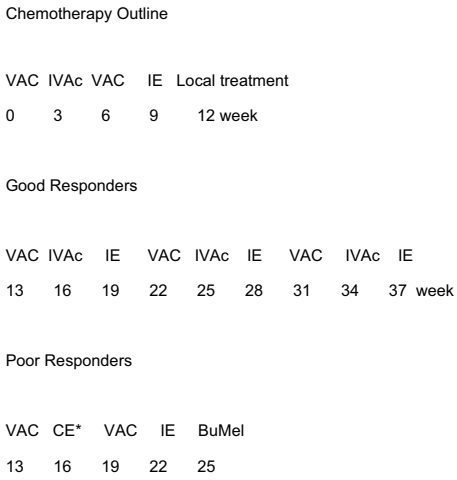

Figure 1. Italian Sarcoma Group/Scandinavian Sarcoma Group III. V, vincristine1.5 mg/m^2 (top dose 2 mg); A, doxorubicin 80 mg/m^2; C, cyclofosfamide 1200 mg/m^2; Ac, actinomycin D1.5 mg/m^2; I, ifosfamide 9 g/m^2, E, etoposide 450 mg/m$^{2;}$ CE*, cyclophosphamide 4 g/m^2 and etoposide 600 mg/m^2; BuMel, busulfan 4mg/kg × 4 days orally and melphalan 140 mg/m^2.

Radical and wide margins were considered adequate, while marginal, intralesional and contaminated margins were inadequate [22].

Chemotherapy-induced tumor necrosis was evaluated according to a method previously reported [12]. When macroscopic foci of viable tumor cells were present, pathologic regression was graded I, when isolated microscopic nodules of viable tumor cells were detected, it was graded II and in absence of viable tumor, it was graded III. Patients with pathologic response grades II and III were classified as GR and PR were grade I.

When pathologic response was not assessable, response to primary chemotherapy was based on radiological response. A retrospective ISG/SSG analysis of combined histological and radiological evaluation of 55 patients revealed a strong correlation between total disappearance of the soft tissue component and a good histological response [23]. Therefore, complete disappearance of the soft tissue component identified GR patients.

statistical analysis

Aims of the study were to evaluate event-free survival (EFS) in patients with nonmetastatic EFT receiving a treatment based on primary chemotherapy response, to assess chemotherapy-induced tumor necrosis and to correlate chemotherapy response to survival. EFS was defined as the period from the start of chemotherapy to the most recent follow-up or local or systemic recurrence or death from treatment-related complications or secondary malignancy. Overall survival (OS) was calculated from the start of chemotherapy to the most recent follow-up or death. Survival curves were calculated according to the Kaplan and Meier method and compared using the log-rank test. Analysis of toxicity was carried out by means of chi-square test or Fisher's exact test.

results

From June 1999 to December 2006, 300 patients from eight centers in Scandinavia and seven centers in Italy entered the study. Follow-up data were updated to June 2009. Patient characteristics are reported in Table 1. Median age was 15 years and 38% of patients were adults (18 years or older). There was a male predominance. The most frequently involved sites were femur, pelvis, tibia and humerus. Overall, 53% of EFT were

located in an extremity, 28% had an axial location and 19% were pelvic.

In 15 cases, diagnosis was made after inadequate surgery for a lesion deemed as benign or after laminectomy for neurological complications secondary to the spine location of the tumor. In all cases, a persistence of soft tissue component was documented before study entry.

Overall, 242 (81%) patients underwent surgery, 12 had a limb amputation, 1 had a rotation plasty and 229 (95%) were resected.

In two children, on demand of the surgeon in order to carry a surgical reconstruction to save the growth plate, surgery was postponed after chemotherapy completion. In six patients, all with pelvic tumors, full-dose radiotherapy was given after primary chemotherapy and surgery was delayed after chemotherapy completion. Of the 15 cases treated with surgery before the beginning of systemic therapy, 10 patients received radiotherapy as definitive local treatment, 4 underwent a subsequent tumor resection and 1, a 4-year-old boy with the tumor located to the spine who achieved complete radiologic response, did not receive further local therapy.

All patients who received up-front surgery had intralesional surgical margins. Evaluation of surgical margins was carried out in 219 of the remaining patients. One hundred and seventy-seven (81%) patients had adequate margins, 32 (15%) marginal and 10 (5%) intralesional.

Overall, 80 patients underwent surgery and radiotherapy. In addition to the 10 patients who underwent immediate surgery, postoperative radiotherapy was given to the 42 patients with inadequate surgical margins and, on a clinical basis, radiotherapy was added in 22 patients whose tumor was resected with clean margins. In six patients, full-dose radiotherapy was given after primary chemotherapy and surgery was carried out after chemotherapy completion. Radiotherapy only was used in 57 (19%) patients. Overall, the median received dose of radiotherapy was 54 Gy (36–64 Gy). In case of radiotherapy only, it was 54 Gy (36–54 Gy) and 45 Gy (41–61 Gy) in surgically treated patients. The median received dose was 54 Gy (41–64 Gy) in patients who received high-dose therapy with busulfan and melphalan.

One patient refused local treatment and received chemotherapy only.

Type and timing of local treatment has been summarized in Figure 2.

Tumor site significantly ($P < 0.001$) influenced the method of local control. Surgery alone was more frequently used in extremity located tumors (surgery 79%, surgery and radiotherapy 18% and radiotherapy 3%), and radiotherapy was more frequently used for pelvic lesions (surgery 25%, surgery and radiotherapy 18% and radiotherapy 57%), whereas tumors with central locations were more likely to receive surgery and radiotherapy (surgery 27%, surgery and radiotherapy 48% and radiotherapy 25%).

Overall, 146 (49%) patients were classified as GR to primary chemotherapy. Six (2%) patients did not complete primary chemotherapy due to local or systemic tumor progression. The remaining 148 (49%) patients were classified as PR to primary chemotherapy.

Evaluation of histological response to primary chemotherapy was carried out in 220 patients who received surgery at the time scheduled by the protocol (i.e. after the four courses of primary treatment). Tumor necrosis was grade I in 110 (50%), grade II in 46 (21%) and grade III in 64 (29%) patients. Histological response was not assessed in three patients who were treated as GR as a result of the radiographic response evaluation. Histological assessment of the response was not applicable in 8 patients who received surgery at the end of the chemotherapy and in 10 who received surgery up front.

A good response was more frequently observed in children, female and patients with an extremity location of the tumor (Table 2).

The type of local treatment significantly ($P = 0.001$) differed according to tumor response: surgery only, combined treatment of surgery and radiotherapy and radiotherapy only were used in 66%, 18% and 16% of patients with a good response, respectively. In those patients with a poor response, the percentages were 44%, 34% and 22%, respectively.

At a median follow-up of 64 months (range 21–116 months), 209 (70%) patients were continuously event free. No acute treatment-related deaths were registered. One patient died of sepsis after pneumonia, 10 months after HDT completion. Acute myeloid leukemia developed in two patients, 13 and 20

Table 1. Patient characteristics

Characteristics	*n* (%)
Age (years)	
Median (minimum–maximum)	15 (3–40)
Age groups (years)	
3–9	51 (17)
10–17	136 (45)
≥18	113 (38)
Sex	
Male	192 (64)
Female	108 (36)
Site	
Femur	49 (16)
Pelvis	56 (19)
Tibia	38 (12)
Humerus	29 (10)
Rib	26 (9)
Spine	24 (8)
Soft tissues	19 (6)
Scapula	15 (5)
Fibula	14 (5)
Other	30 (10)
LDH[a]	
Normal	181 (68)
High	84 (32)
SAP[b]	
Normal	239 (89)
High	29 (11)

[a]Available in 265 patients.
[b]Available in 268 patients.
LDH, lactate dehydrogenase; SAP, serum alkaline phosphatase.

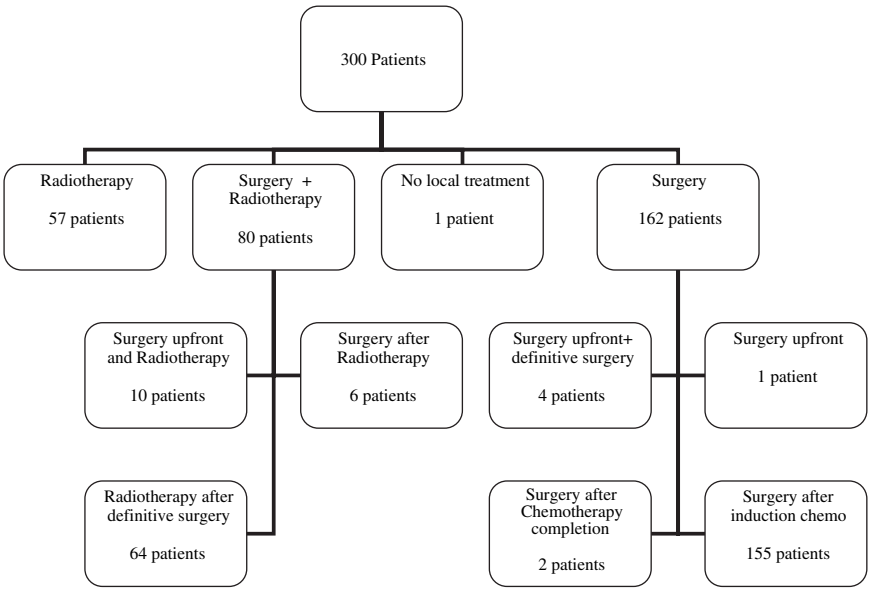

Figure 2. Type and timing of local treatment.

Table 2. Response to primary chemotherapy according to clinical characteristics

	GR (%)	PR (%)	*P* value
Gender			0.04
Male	85 (44)	107 (56)	
Female	61 (56)	47 (44)	
Age (years)			<0.001
3–9	36 (71)	15 (29)	
10–17	74 (54)	62 (45)	
≥18	36 (32)	77 (68)	
Site			0.05
Extremity	86 (54)	73 (46)	
Central	60 (43)	81 (57)	
SAP[a]			0.9
High	14 (48)	15 (52)	
Normal	113 (47)	126 (53)	
LDH[b]			0.3
High	44 (52)	40 (48)	
Normal	81 (45)	100 (55)	

[a]Available in 268 patients.
[b]Available in 265 patients.
GR, good responders; LDH, lactate dehydrogenase; PRs, poor responders; SAP, serum alkaline phosphatase.

months after chemotherapy completion (both patients received surgery as local therapy: one had a good histological response and the second had poor histological response, but he refused high-dose treatment and completed chemotherapy with the same scheme used for GR). Local disease progression alone was documented in 14 patients; bone metastases and lung metastases were reported in 15 and 21 patients, respectively. In 36 patients, tumor recurrence involved multiple sites. Insufficient data were available to define the pattern of recurrence in two patients.

The 5-year EFS rate was 69% [95% confidence interval (CI) 63% to 74%]. The 5-year OS rate was 75% (95% CI 70% to 80%). Table 3 reports the probability of EFS according to different variables.

According to response to primary chemotherapy, patients with good response had a 5-year EFS rate of 75% (95% CI 68% to 82%) and the remaining patients had a 5-year EFS rate of 63% (95% CI 55% to 70%).

Overall, 154 patients were classified as PR patients. Twenty-eight patients did not receive HDT. Ten patients had tumor progression during standard chemotherapy, four (three males aged 13, 15 and 22 years, respectively, and one female 21 years old) had poor harvest of CD34+ cells, four refused the procedure, three had medical contraindications (one male 6 years old with radionecrosis of the chest wall, one male 19 years old with Bullous pulmonary lesions and one female 26 years old with aortic insufficiency) and seven were excluded on a clinical basis of the treating center. All patients completed the chemotherapy program as GR.

The probability of 5-year EFS for the 126 PR patients who could intensify treatment with HDT was 72% (95% CI 64% to 80%). PR patients who were given standard chemotherapy had a 5-year EFS of 33% (95% CI 11% to 55%) (Figure 3).

toxicity

No toxic deaths were reported. One patient died of sepsis, 10 months after HDT completion, but the relationship with chemotherapy was not proven.

After conventional VAC-IVAc-IE courses, grade 4 leukopenia and thrombocytopenia were 66% and 7%, respectively. Overall, hospitalization for chemotherapy toxicity was needed after 17% of courses.

After the mobilizing course CE, all patients experienced grade 4 leukopenia (neutropenic fever in 38%) and 45% grade 4 thrombocitopenia. Red blood cell or platelet transfusions

Table 3. EFS probability

Variable	% 5-year EFS (95% CI)	*P* value
Age (years)		0.04
3–9	77 (65–89)	
10–17	71 (64–79)	
≥18	62 (52–71)	
Sex		0.9
Male	68 (62–75)	
Female	69 (60–78)	
Site		0.8
Extremity	68 (60–75)	
Central	72 (62–82)	0.8
Pelvis/sacrum	67 (55–80)	
LDH[a]		0.005
Normal	73 (67–80)	
High	58 (48–69)	
Local treatment		0.001
Surgery	71 (64–78)	
Surgery and radiotherapy	76 (66–85)	
Radiotherapy	53 (40–66)	
Response		0.01
Good response	75 (68–82)	
Poor response[b]	63 (55–70)	

[a]Available in 265 patients.
[b]Including patients who progressed during primary chemotherapy.
CI, confidence interval; EFS, event-free survival; LDH, lactate dehydrogenase.

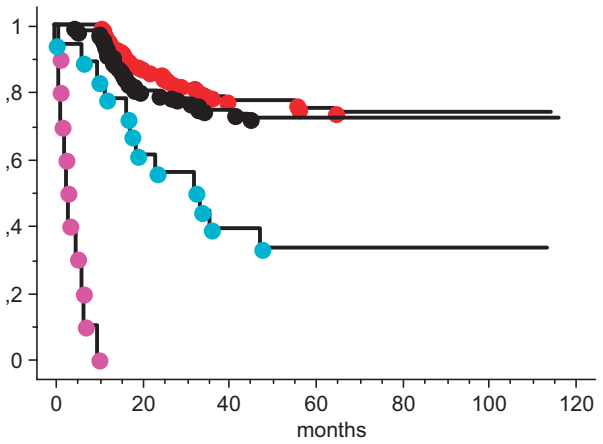

Figure 3. Event-free survival according to response to primary chemotherapy and to high-dose chemotherapy.

were required in 66% and 40% of courses. The median CD34+ collected cells were 7.2 × 106/kg (range 1.4–23).

After HDT, 94% of patients had grades 3–4 mucositis, red blood cell (77%) or platelet (95%) transfusions were required for most patients. The median time to reach a platelet count >50 × 10^9/l and leukocyte count >1.5 × 10^9/l were13.5 (9–40) and 11 (4–38) days, respectively. Epileptic seizures were reported in one patient. Transient laboratory findings suggesting a hepatic veno-occlusive disease were reported in six patients. Permanent gonadal damage was observed in all postpuberal patients who underwent high-dose therapy.

Four PR patients experienced a remarkable radiotherapy toxicity. One patient after chest wall irradiation developed a severe radionecrosis, which did not allow the use of high-dose therapy. Two patients had a radiation-induced colitis requiring partial colectomy. One patient was treated locally with surgery and radiation therapy (total dose 45 Gy) and the other with radiation therapy alone (total dose 54 Gy). One patient with tumor located to the thoracic spine had transverse myelitis after radiotherapy (total dose 42 Gy). The three former patients received intensified treatment with HDT.

discussion

ISG/SSG III was a joint study aimed to explore survival in patients with nonmetastatic ES treated with a chemotherapy-adapted protocol based on the response to induction chemotherapy.

The histological response to primary chemotherapy is the main predictive factor of survival in localized EFT. In the French experience, patients with a good histological response had a probability of 5-year EFS of 75% compared with 40% and 20%, respectively, for intermediate or poor histological response [9]. Final results of the CESS-86 study reported a 10-year probability of EFS of 64% for patients with a good histological response and 38% for PR patients [7]. In the Italian experience, the reported 10-year EFS was 75% in GR patients compared with 27% in PR patients [4].

Different strategies of treatment are certainly needed in PR patients.

In the last years, interesting and promising results have been reported by the use of HDT and peripheral blood stem cell rescue in patients with ES.

The first experience was reported in the 1988 [13] in patients with metastatic disease. Afterward, several papers described the use of HDT in high-risk (synchronous metastases or recurrent disease) patients with EFT [13–21]. The results were contradictory with some reports [15, 18, 21], suggesting an activity of megatherapy in EFT, but the scientific community has not yet reached an agreement on the use of HDT in EFT. Since 1999, a randomized trial whose main objective is to establish the role of megatherapy in EFT is ongoing [24]. More recently, the activity of HDT in patients with EFT has been described in two European studies: the first included patients with recurrent disease and the second with synchronous metastatic disease [25, 26].

ISG and SSG agreed on the clinical relevance of the effectiveness of HDT in high-risk EFT patients. The strategy of treatment was characterized by the selective use of HDT in patients with poor response to primary chemotherapy based on the VACA/IE regimen. Protocol INT-0091 (CCG-7881 and POG-8850) [8] had clearly shown that the VACA/IE regimen was more effective compared with the VACA regimen. A Rizzoli monoinstitutional study carried out in the early nineties showed that in spite of the primary use of the VACA/IE regimen, only 50% of patients obtained a good histological response [27]. The present multicentric study confirmed these data.

In the ISG/SSG III study, a relation between age and chemotherapy-induced tumor necrosis was observed. Children (age < 18 years) were more likely to have a good response to primary chemotherapy than adults. These data confirm those reported in a retrospective monoinstitutional analysis [28].

For different reasons, 19% of PR patients could not be given the planned chemotherapy with high-dose treatment. Ten patients did not receive HDT due to tumor progression during standard chemotherapy and eventually died of diseases within 12 months from tumor progression. It is interesting to note that the remaining PR patients who did not receive HDT had a probability of 5-year EFS of 33% (95% CI 11% to 55%). This percentage is in the same range as that previously observed in studies in which PR patients received conventional chemotherapy [4, 7, 9].

A major observation from this study is that PR patients who received HDT had a 5-year EFS of 72% (95% CI 64% to 80%), similar to the 5-year EFS of 75% achieved in GR patients.

The results of our study confirm the importance of the response to primary chemotherapy in EFT and suggest that a strategy of salvage chemotherapy in PR patients is feasible and effective. Overall, the reported results are better than those obtained in previous SSG and ISG experience [4, 29, 30].

The present data do not come from a randomized study and the comparison with the group of patients who could not receive HDT in ISG/SSG III study and that with historical series are not statistically adequate. For this reason, they should be considered with caution.

No treatment-related deaths were recorded. Previous large multicentric studies with conventional chemotherapy reported an incidence of toxic deaths ranging from 0.6% to 3% [8, 31, 32]. In our opinion, the decision of centralizing patients in referral centers has certainly contributed to the feasibility of the treatment. Some cautions should be addressed to the potential additional risk in terms of late side-effects, namely possible higher incidence of second malignancies by the use of high-dose therapy. Furthermore, the gonadal failure is a high price that patients undergoing such a sterilizing treatment have to pay. Sperm banking in men and cryopreservation and reimplantation of ovarian tissue in women are recommended procedures that may reduce the impact of the expected infertility in patients undergoing high-dose treatment.

A probability of EFS at 5 years ~70% has been reported with protocols based on conventional chemotherapy [8, 31]. In our opinion, it is important to underline that the adult population included in the cited studies was only 13%–14%, respectively [8, 31], and that the study population was dominated by pediatric patients, who it well recognized, have better prognosis in EFT [4, 9, 10], whereas in the ISG/SSG III study, 40% of the population were adults (age > 18 years).

If we compare our results with those of a recent European multicentric study, with conventional chemotherapy, a 5-year EFS close to 70% is reported only for a minority (155 of 647, 24%) of patients having small tumors and classified as standard-risk patients, whereas a 5-year EFS <60% was reported for the remaining localized patients [32].

In conclusion, the present study showed that the use of HDT in PR patients to the VACA/IE regimen is feasible and effective. The probability of survival obtained with this study in PR patients is higher than that obtained in historical series. The present data support the use of HDT in selected risk groups of EFT patients.

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disclosure

The authors declare no conflict of interest

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